

## CASE REPORT

# Crizotinib-associated renal cyst development may be associated with prolonged progression-free survival in patients with *ALK*-positive non-small-cell lung cancer: Case report and review of the literature

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## Funding information

The authors received no financial support for the research and authorship of the article. Departmental funds (RM) were used to support publication of this report

## Abstract

Non-small cell lung cancer patients with anaplastic lymphoma kinase or c-ros oncogene 1 mutations who are treated with the tyrosine kinase inhibitor crizotinib rarely develop crizotinib-associated renal cysts (CARCs). Here, we present a case report and review of the literature supporting the hypothesis that CARCs may correlate positively with progression-free survival.

## KEYWORDS

ALK positive, crizotinib, non-small-cell lung cancer, progression-free survival, renal cysts

## 1 | INTRODUCTION

Crizotinib is an orally administered anaplastic lymphoma kinase (ALK) inhibitor that has received approval from the Food and Drug Administration (FDA) for the treatment of *ALK*-positive non-small cell lung cancer (NSCLC) in November 2013 after a Phase 3 trial comparing crizotinib to chemotherapy in advanced or metastatic *ALK*-positive lung cancers, which demonstrated a significant improvement in

progression-free survival (PFS) from 3.0 to 7.7 months in the crizotinib arm.<sup>1</sup> Crizotinib is a receptor tyrosine kinase inhibitor (TKI) that blocks the signaling of ALK, hepatocyte growth factor receptor (HGFR or c-Met), Recepteur d'Origine Nantais (RON), and c-ros oncogene 1 (ROS1).<sup>2,3</sup> While next-generation ALK TKIs such as alectinib and brigatinib have now shown better efficacy than crizotinib in the first-line setting for *ALK*-positive NSCLC,<sup>4</sup> crizotinib is still prescribed for some patients with *ALK*-positive advanced NSCLC

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including patients who have continued to be on it since the days when it was the only available and approved treatment. Further, crizotinib continues to be a standard-of-care first-line treatment for patients with *ROS1*-positive advanced NSCLCs and has also shown efficacy and is prescribed to some patients with *MET* exon 14 skipping mutations.<sup>3,5</sup> In addition, crizotinib is currently under study internationally in 76 clinical trials (either pre-recruiting, recruiting, or active and completed recruiting) listed on clinicaltrials.gov as of time of publication.

It was recognized in early clinical trials utilizing crizotinib to treat *ALK*-positive or *ROS1*-positive NSCLC that a proportion of crizotinib-treated patients developed renal cystic changes. In the PROFILE 1001, PROFILE 1007, and PROFILE 1014 trials, renal cysts were reported as an adverse event in 3%-5% of patients.<sup>6</sup> Three subsequent radiological reviews found that 16%-42% of crizotinib-treated patients developed either de novo renal cysts or changes in preexisting renal cysts, with 4%-27% of patients experiencing complex cystic changes concerning for malignancy.<sup>7-9</sup>

Crizotinib-associated renal cysts (CARCs) are de novo renal cysts that develop while on treatment with crizotinib. CARCs demonstrate heterogeneous behaviors—some CARCs resolve while patients remain continuously on crizotinib, whereas many require discontinuation or changes in therapy (Table 1). A minority of CARCs demonstrate invasive behavior and can exceed the renal cortex to invade nearby structures including the perinephric space, psoas muscles, intestines, and abdominal wall.<sup>10</sup> Published biopsy results for CARCs have consistently demonstrated fibrous or granulomatous tissue negative for malignancy (Table 1), with no published reports of CARCs containing metastatic NSCLC, to the knowledge of these authors.

The biology of CARCs is not well-understood. While Halpenny et al<sup>9</sup> found preexisting renal cysts to be a risk factor for CARC development or cystic changes, Lin et al<sup>7</sup> did not find this association to be statistically significant. Schnell et al<sup>10</sup> analyzed patients in whom renal cysts were reported as a serious adverse event in clinical trials and found a significant association between renal cyst development and Korean race, suggesting a genetic predisposition. Notably, Yasuma et al utilized a rodent model of crizotinib administration to study pathways altered in the kidneys of crizotinib-exposed mice. They found that crizotinib induced mesangial expansion and fibrosis of rodent kidneys and correlated these changes with activation NF- $\kappa$ B and TNF $\alpha$ , providing mechanistic insights into cell signaling changes that occur in crizotinib-exposed renal tissue.<sup>11</sup>

The fact that CARCs and crizotinib-associated renal cystic changes are nonmalignant and should be managed without surgical intervention, despite their concerning appearance on imaging, is highlighted throughout the published studies. However, it is unknown whether the

development of CARCs is correlated with the clinical course of cancer being treated.

Here, we present the case of a patient with *ALK*-positive NSCLC who developed a symptomatic CARC and experienced an exceptional progression-free survival (PFS) of 36.9 months. We review the literature on CARCs and provide preliminary evidence that patients who develop CARCs may experience longer PFS than expected.

## 2 | CASE PRESENTATION

A 67-year-old Caucasian female patient with no known renal disease and a 30-pack-year history of cigarette smoking under active surveillance for right lung nodules developed a right-sided pleural effusion that was found to contain atypical cells suspicious for adenocarcinoma. PET-CT was performed and demonstrated multiple confluent, hypermetabolic nodules in the right lower lobe with potential pericardial involvement and a hypermetabolic right upper lobe nodule (Figure 1A,C). Endoscopic ultrasound with fine-needle aspiration of right-sided enlarged peribronchial lymph nodes demonstrated adenocarcinoma with low expression of PD-L1. Given her probable malignant pleural effusion, she was diagnosed with likely Stage IV NSCLC, and treatment with carboplatin and pemetrexed was initiated, while samples were sent for genetic analysis, which at the time required significantly more time than present to obtain results.

After the first cycle of chemotherapy, the patient's tissue genomic testing resulted in *EML4-ALK* fusion, *NFKBIA* amplification, and *NKX2-1* amplification. Given the *ALK* fusion result, her regimen was switched to crizotinib 250 mg daily. PET-CT 2 months after initiation of crizotinib demonstrated a very good partial response to therapy (Figure 1B,D). The patient tolerated crizotinib well and enjoyed a sustained disease response. However, 17.9 months after initiating crizotinib, a heterogeneous, 2.8-cm right cystic mass consistent with a CARC was noted (Figure 2A). This mass increased in size and invaded the right psoas muscle over the next 5 months (Figure 2B), accompanied by the development of right flank pain, subjective fevers, and poor appetite. Over this period, the patient experienced an 8.3 kg weight loss, as well as mild thrombocytosis, erythrocytopenia, and hypoalbuminemia (Figure 3). Other cell counts including lymphocytes, neutrophils, and eosinophils did not show alterations. As imaging raised the possibility of malignancy as opposed to CARCs, two biopsies were performed at two subsequent times and were both negative for malignancy and demonstrated granulation tissue (Figure 4).

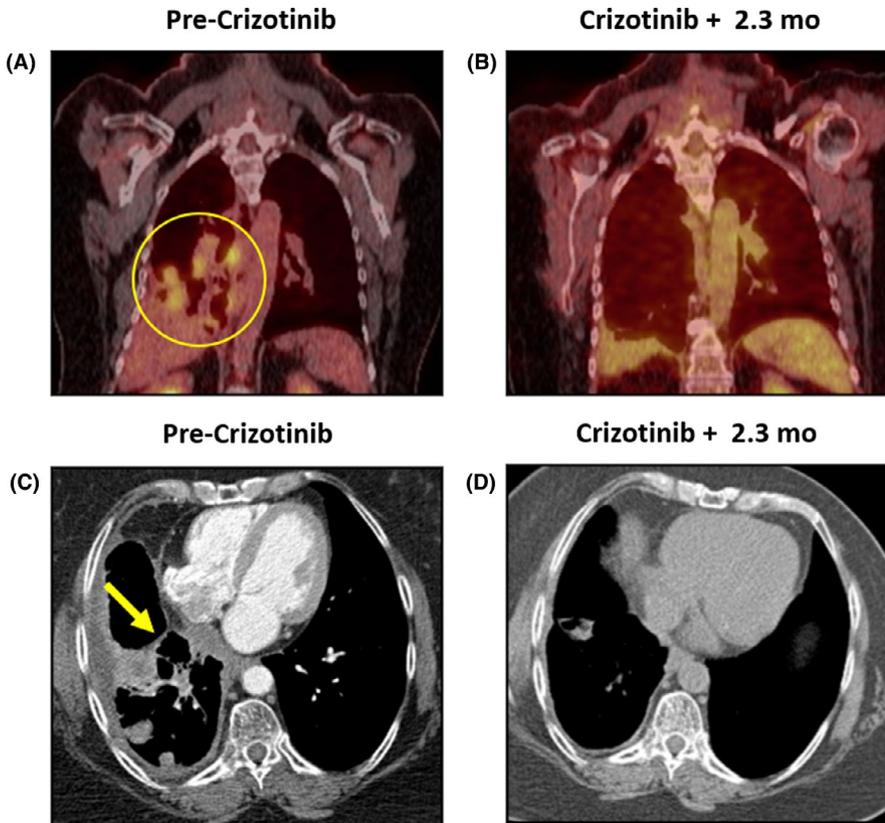
Despite the negative biopsies, the aggressive, symptomatic, and invasive nature of the CARC was initially considered suspicious for malignancy by a multidisciplinary tumor board, given rare reports of renal NSCLC metastases,<sup>12</sup> and

**TABLE 1** Case reports of CARCs in patients with ALK-positive NSCLC

Reference	Age (y)	Gender	NSCLC stage	Time to CARC (m)	CARC laterality	Bosniak class	CARC pathology	Outcome	PFS (m)
This study	67	F	IIIB or IV	17.9	Right		Biopsy showed granulatum tissue negative for malignancy	Crizotinib discontinued with regression of CARC	36.9
Klempner et al 2014	49	F	-	6	Bilateral	IIF	-	Crizotinib continued with spontaneous regression of CARCs	31 <sup>a</sup>
Di Girolamo 2015	71	M	IV	-	Bilateral	IIF or III	Biopsy showed fibrous tissue with chronic inflammation negative for malignancy	Therapy switched to certinib with regression of CARCs	-
Chan 2016	68	F	IIIA	7	Right	III	Cyst aspiration negative for malignancy or infection	Crizotinib discontinued. CARC eventually resolved after drainage	-
Yoneshima 2015	39	F	IIIB	6	Left	-	Cyst aspiration showed neutrophils and degenerated material negative for malignancy	Crizotinib discontinued. CARC resolved after drainage	-
Taima 2017	56	M	-	10	Right	-	Biopsy showed granulomatous inflammation negative for malignancy	Therapy switched to alectinib with regression of CARC	23
Okubo 2018	77	M	-	4	Bilateral	III	-	Crizotinib discontinued with regression of CARCs	-
Yasuma 2018	71	F	-	11	Right	-	Cyst aspiration negative for malignancy or infection	Therapy switched to alectinib with regression of CARCs	-
Liaw 2019	53	F	-	-	Right	-	Biopsy showed granulomatous inflammation negative for malignancy	Therapy switched to alectinib with regression of CARCs	-
Okauchi 2019	38	M	IIIA	5	Right	-	-	Crizotinib continued with spontaneous regression of CARCs	17 <sup>a</sup>
Di Marino 2020	74	F	IV	8	Bilateral	-	-	Therapy switched to alectinib with regression of CARCs	16 <sup>a</sup>
			Median time to CARC	7.0 ± 4.2 months				Median PFS	23.0 ± 8.6 months

Note: denotes not reported.

<sup>a</sup>denotes response ongoing at the time of publication of study.



**FIGURE 1** Positive response to crizotinib targeted therapy. Fused retrocardiac sagittal PET-CT images before A, and 2 months after B, crizotinib initiation demonstrate resolution of right-sided hypermetabolic foci (circle). Axial CT images before C, and after D, crizotinib initiation demonstrate resolution of multiple right-sided mass-like opacities, as well as resolution of associated pleural thickening and possible pericardial invasion (arrow)

surgical intervention was scheduled. Prior to surgery, crizotinib was discontinued, given published reports of CARCs that resolved after crizotinib discontinuation (Table 1). The day before planned surgery, approximately 5 weeks after stopping crizotinib, imaging demonstrated regression of the CARC, and surgery was cancelled. The patient's flank pain and subjective fevers subsequently resolved, the lesion rapidly regressed (Figure 5), and her weight and laboratory anomalies normalized (Figure 3).

Our patient was treated with crizotinib for a total of 23.4 months. After development, the invasive CARC grew rapidly as assessed by volumetric measurements, followed by even more rapid resolution after crizotinib discontinuation (Figure 5). She remained off crizotinib for 13.9 months until disease progression with MRI-demonstrated brain parenchymal lesions at which point therapy was switched to alectinib. Her total PFS after starting crizotinib, including time off therapy after CARC development, was 36.9 months.

### 3 | RESULTS FROM PFS ANALYSIS IN THE PUBLISHED LITERATURE

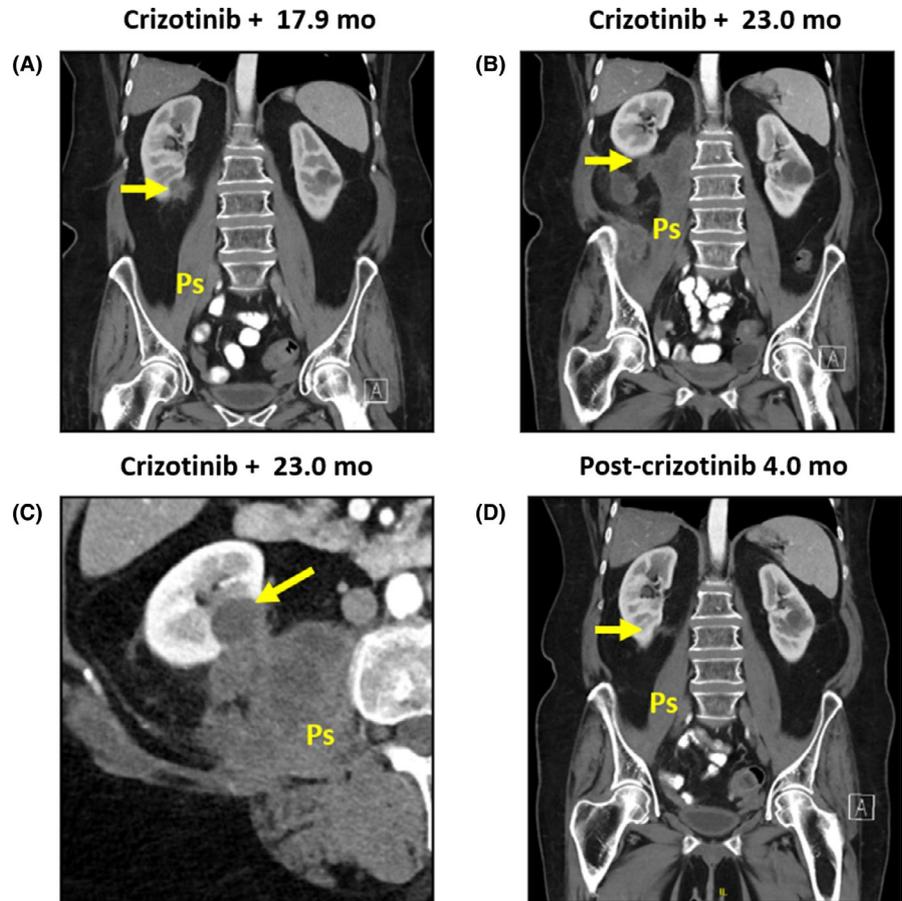
A literature search was performed for all published reports of crizotinib-associated renal cystic changes and CARCs in patients with *ALK*-positive NSCLC. Ten case reports were identified (Table 1). Four of 10 case reports with detailed

PFS data that, when combined with data from this case, yielded a median PFS of  $23 \pm 8.6$  months in *ALK*-positive NSCLC patients treated with crizotinib who developed CARCs ( $n = 5$ , data  $\pm$  one standard deviation). Five multi-patient studies of crizotinib-associated renal cystic changes in patients with *ALK*-positive NSCLC were also identified (Table 2). Quantitative PFS data were only described in Lin et al<sup>7</sup>, which reported increased PFS in patients with significant renal cystic changes on crizotinib that trended towards statistical significance (509 days versus 210 days,  $P = .09$ ). A qualitative analysis of Schnell et al revealed that 15/16 patients who developed renal cysts on crizotinib had a PFS longer than 7.7 months and 11/16 had a PFS longer than 13.0 months, indicating that a majority of these patients experienced PFS for longer than the published range of PFS in *ALK*-positive NSCLC of 7.7-13.0 months.<sup>1,13,14</sup> The remaining studies did not provide quantitative or qualitative data regarding PFS.

### 4 | DISCUSSION

Crizotinib was the first FDA-approved receptor TKI targeting *ALK* for use in advanced NSCLC, and its introduction more than doubled PFS at the time.<sup>1</sup> TKIs including crizotinib have revolutionized the treatment of many cancers by providing a rational means to target specific cell signaling pathways that cancers rely on for growth and survival.<sup>15</sup> However, the

**FIGURE 2** Crizotinib-associated complex renal cyst development and regression. Coronal venous-phase CT images upon the first observation of the complex right renal cyst (A, 17.9 months after initiation) and 5 months later B, show enlargement and invasion of the right psoas muscle. An axial slice of the lesion demonstrates multiple septations and invasion of the psoas muscle C. Repeat CT 4 months after discontinuation of crizotinib demonstrates rapid regression of the lesion D. Arrow = right renal complex cyst. Ps = psoas muscle



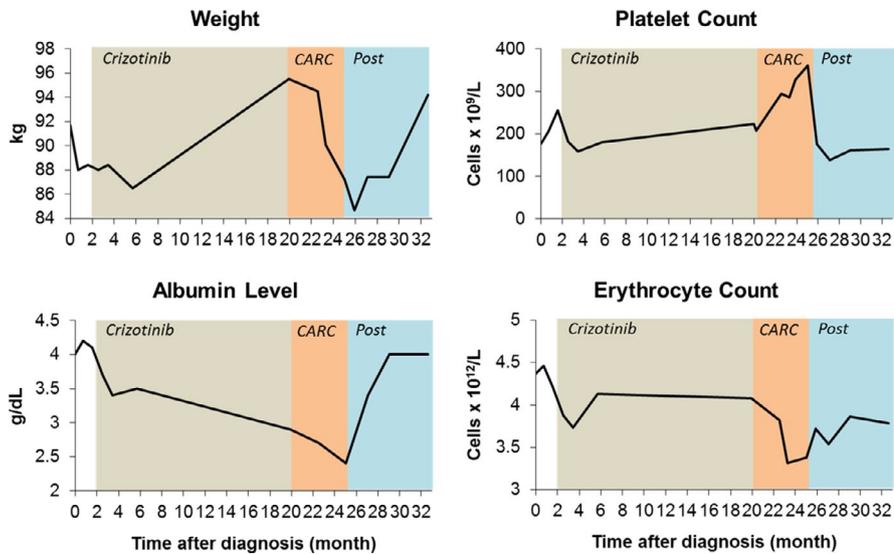
fact that TKIs target cellular signaling pathways involved in a large number of cellular processes can lead to the generation of diverse and atypical side effect profiles. While generally well-tolerated, 38.1% of patients taking crizotinib will develop a grade 3 or above adverse event,<sup>16</sup> including CARCs.

Our report is novel in describing sustained PFS even after discontinuation of all anticancer therapies in a patient with *ALK*-positive NSCLC who developed a CARC. The exceptional nature of her response, combined with the fact that she developed a CARC, led us to hypothesize that CARC development may positively correlate with PFS in patients with *ALK*-positive NSCLC. Our analysis of the published literature described previously provides preliminary support for this hypothesis, though the limited available data and heterogeneous case reporting preclude the ability to draw conclusions at this point and emphasize the need for larger studies to better address this question. If further studies support this hypothesis, then this would assign novel prognostic value to CARCs.

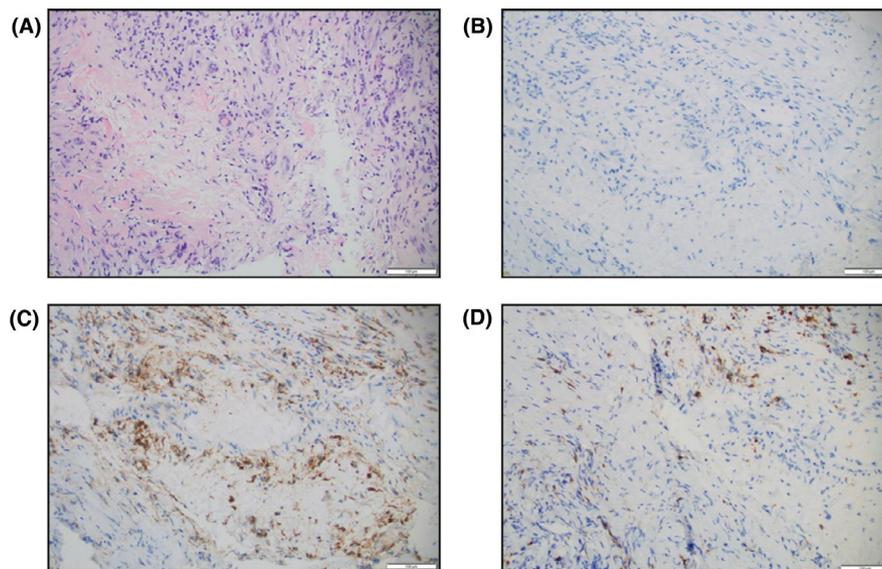
An alternative hypothesis we considered was that patients who experience extended PFS on crizotinib may develop CARCs because of their prolonged drug exposure. However, we note that many CARCs develop early in treatment, with a median time to CARC development in the published case reports of 7.0 months (Table 1), which falls within the range

of PFS in *ALK*-positive NSCLC patients treated with crizotinib of 7.7-13.0 months.<sup>1,13,14</sup> As such, current evidence indicates that CARCs develop within a standard time frame of crizotinib treatment. As more reports and larger studies of CARCs in *ALK*-positive NSCLC and other malignancies are published, this will allow a better assessment of the temporal relationship between CARC development and PFS.

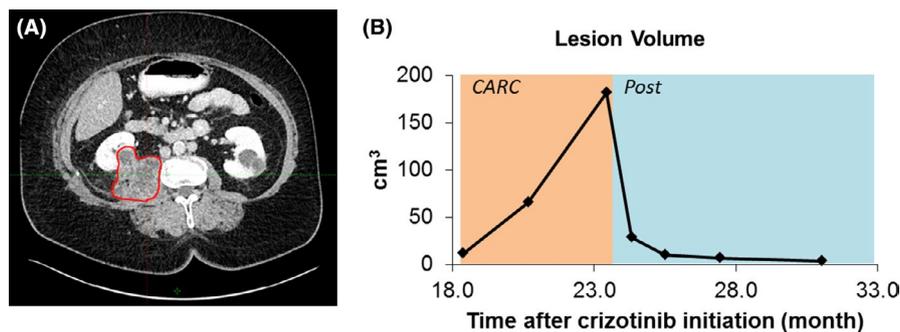
There is precedence for adverse effects of TKIs correlating with improved survival. A multivariate analysis of RCC patients treated with sunitinib and sorafenib identified higher grade clinical toxicities (grade 3-4) as an independent prognostic factor for better survival.<sup>17</sup> A meta-analysis of epidermal growth factor receptor (EGFR) TKIs identified that PFS was significantly increased in patients who developed skin rash.<sup>18</sup> TKI-associated diarrhea and hypertension have been associated with positive outcomes in hepatocellular carcinoma.<sup>19</sup> Of course, TKI adverse effects are not uniformly associated with survival and have been demonstrated to decrease survival in contexts such as chronic myelogenous leukemia.<sup>20</sup> As such, it is likely that whether TKI adverse effects correlate with survival depends on the specific adverse effect and the underlying malignancy, and likely reflects interactions between TKI pharmacodynamics, tumor biology, and underlying patient characteristics.



**FIGURE 3** Perturbations in patient biometrics during complex right renal cyst development. Indicated patient biometric data plotted. Of note, other cell counts (neutrophils, lymphocytes, and monocytes) were not significantly altered by crizotinib-associated renal cyst (CARC) development and are not shown. *Crizotinib* = time period after crizotinib initiation but before CARC development on imaging. *CARC* = time period during which CARC was observed. *Post* = time period post-crizotinib discontinuation



**FIGURE 4** Crizotinib-associated renal cyst pathology demonstrated granulation tissue. Biopsies demonstrate granulation tissue as demonstrated by a loosely cohesive lymphohistiocytic proliferation. A, Zones of edema and thin-walled delicate vessels that are characteristic of this process. B, Pan cytokeratin stain is negative; this is a pertinent negative, given the patient's history of carcinoma. C, Histiocytes are positive for CD68, as shown in panel C. D, Characteristically, the lymphocytes associated with granulation tissue tend to be T-cell-rich as demonstrated by the CD3 immunostain in panel D (CD20 not shown). Taken together, these findings are diagnostic for granulation tissue



**FIGURE 5** Volumetric assessment of right-sided complex renal cyst. A, Axial CT image demonstrating contouring (red line) of the right-sided complex crizotinib-associated renal cyst (CARC). B, Lesion volumes demonstrated a rapid decrease after crizotinib discontinuation. *CARC* = time period during which CARC was observed. *Post* = time period post-crizotinib discontinuation

**TABLE 2** Multipatient studies of CARCs in patients with ALK-positive NSCLC

Reference	Study design	Findings relevant to PFS in patients with CARCs	Limitations
Lin et al 2014	Cohort study of 32 patients receiving crizotinib who were routinely followed up with high-resolution abdominal CT scans	PFS in patients with significant renal cystic changes 509 days versus 210 days in patients without renal cyst changes ( $P = .09$ )	Results not significant due to small number of patients
Schnell et al 2015	Retrospective radiological review of 17 patients who had renal cysts reported as serious adverse events (SAEs) across four clinical trials	15/16 patients with renal cysts reported as SAEs remained on crizotinib therapy longer than 7.7 months, and 11/16 longer than 13.0 months <sup>a</sup>	PFS not reported. Time on crizotinib not reported
Cameron et al 2017	Retrospective radiological review of 26 crizotinib-treated patients at a single center	-	PFS not reported. Time on crizotinib not reported
Halpenny et al 2017	Retrospective radiological review of 60 crizotinib-treated patients at a single center	-	PFS not reported
Eiamprapaporn et al 2019	Case series of 13 patients at a single center	-	PFS not reported

Note: denotes no qualitative or quantitative findings relative to PFS given.

<sup>a</sup>denotes qualitative assessment of Figure 2 in Schnell et al.

**TABLE 3** Recommended minimum information for reporting TKI-associated renal cysts

Patient	Age, gender, race/ethnicity, previous renal cysts
Cancer	Stage at diagnosis, genetic information, treatment history, treatment response, PFS
TKI-associated renal cysts	Time to diagnosis, laterality, pathology (if obtained), symptoms, complications, abnormalities in vitals and labs

There are few reports of CARCs in patients being treated for malignancies other than NSCLC. Yao et al recently reported the case of a patient with carcinoma of unknown origin with *MET* gene amplification who developed a CARC after crizotinib administration.<sup>21</sup> This patient experienced a complete response with a PFS of 8.0 months.<sup>21</sup> As newer clinical trials assess the efficacy of crizotinib in other clinical contexts, this will provide more data to assess the relationship between CARCs and other underlying malignancies.

An open question in the literature is whether TKIs other than crizotinib can cause complex renal cystic changes. The most recent management strategy for CARCs in published reports has been to switch therapy, possibly after improvement or resolving of CARCs, to alectinib (Table 1), which is a TKI in the same family as crizotinib that is not typically associated with renal cystic changes. However, Longo et al recently reported the case of complex renal cysts developing in a patient with *ALK*-positive NSCLC treated with

alectinib.<sup>22</sup> This raises the intriguing possibility that renal cystic changes may be a class effect of ALK-TKIs and not confined to crizotinib alone and emphasizes the importance of monitoring for and reporting adverse effects of targeted therapies.

It is important to note the multiple limitations to our PFS analysis. First, most of the published studies included were case reports (10/15). Of the case reports, only 4/10 reported PFS or sufficient data to determine PFS. Of the remaining five studies, these included one cohort study, one case series, and three retrospective reviews. Out of these studies, only one reported PFS, and three did not give enough information in text to assess PFS. The limited number of studies reporting PFS increases the probability of selection bias, and the heterogeneous reporting between studies limits the ability to assess for correlations.

Given the potential implications of CARCs and similar renal cystic changes with other TKIs including alectinib, there is a need for larger studies to address this topic. We

propose that future studies on CARCs and cystic changes in patients treated with TKIs report a minimum set of information to assess patient, cancer, and CARC characteristics, including PFS (Table 3). This will facilitate a better understanding of the biology and implications of TKI-associated renal cystic changes and help elucidate the properties of these intriguing lesions.

## 5 | METHODS

### 5.1 | Volumetric measurements

Abdominal CT images from different time points were uploaded into Varian Eclipse (version 15.1). Three-dimensional volumes were calculated by contouring the lesion, as illustrated in Figure 5.

### 5.2 | Literature search

An English language search was performed on PubMed and Web of Science (version 5.3.4) using the terms “crizotinib” and “renal cyst” or “renal lesion” from January 2020 to March 2021. All articles were reviewed. Case reports, case series, and retrospective reviews were selected for further analysis and assessment of patient data.

### CONFLICTS OF INTEREST

RM has participated in advisory boards for AstraZeneca, Guardant Health, Novocure, and Takeda. YL has participated in advisory boards for AstraZeneca and Novocure. The other authors declare no potential conflicts of interest.

### ETHICAL APPROVAL

Institutional ethics approval was not required for this study. Consent was obtained from the patient for the reporting of this case.

### AUTHOR CONTRIBUTIONS

NW and RM wrote the article. KT and SH performed volumetric analysis of the lesions. MO performed pathologic analysis. All authors provided significant intellectual contribution.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available on PubMed at <https://pubmed.ncbi.nlm.nih.gov/>.

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**How to cite this article:** Wiest NE, Tzou KS, Olson MT, et al. Crizotinib-associated renal cyst development may be associated with prolonged progression-free survival in patients with *ALK*-positive non-small-cell lung cancer: Case report and review of the literature. *Clin Case Rep.* 2021;9:e04278. <https://doi.org/10.1002/ccr3.4278>